Roger Randal Charles NEW

DECLARATION II

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/019,052
Applicant	: Roger NEW et al.
Filed	: April 22, 2002
TC/A.U.	: 1639
Examiner	: Shibuya, Mark Lance
Docket No.	: 1417-212
Customer No.	: 06449
Confirmation No.	: 5183

DECLARATION UNDER 37 CFR § 1.132

Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Roger Randal Charles NEW, do solemnly declare that:

1. I am of mature age and competent to make this declaration.

2. I am the inventor in this application.

3. I am a graduate in Chemistry from Oxford University UK, and have a PhD in Immunology from London University. I have been working in the area of biological sciences, biotechnology and biopharmaceuticals, in research laboratories, for over thirty years. My CV is attached.

4. I have reviewed and am familiar with U.S. Patent Application Serial No. 10/019,052, filed April 22, 2002, entitled "Epitopes Formed by Non-covalent Association of Conjugates," including the claims currently pending in the application. I also have reviewed and am familiar with the Office Action dated March 13, 2007 and the references cited therein.

5. The Office Action dated March 13, 2007 in the present application Examiner Shibuya rejected claim 32 as being obvious over each of Crabtree et al., Capon et al., or Ueda et al., each taken separately and in view of Onyuksel et al.

6. As explained in the specification, I and my co-inventor have discovered surprisingly that separate

conjugates in a micelle wherein the head groups of separate conjugates are free to move in the micelle and interact cooperatively to form an epitope capable of binding to a ligand provide an improved way to present binding-site epitopes for the development of new receptor-specific therapeutic strategies. As discussed on page 5 of the specification, strong specific binding interactions can be achieved with conjugates in which the head groups are small in comparison to conventional large biological receptor molecules. Accordingly, the micelle according to the present invention can be made far less immunogenic than large proteins. The micelle of the present invention is also easier to manufacture, isolate and maintain in stable form.

6. A skilled person in the art starting from Crabtree, Capon or Ueda in view of the teaching of Onyuksel would have to make a significant number of modifications to the teaching of these documents in order to arrive at the micelle according to claim 32, as discussed below. In my opinion, these modifications would not have been obvious to a person skilled in the art.

7. Firstly, a skilled person would have to modify the proteins of Crabtree, Capon or Ueda to fall within the scope of the conjugates and head groups of the present invention.

8. The description of the present application clearly explains that large proteins are not encompassed by the present invention. Page 1 states that being constrained to large proteins to present binding-site epitopes gives rise to several problems in development of new receptor-specific therapeutic strategies, including an unwanted immune response and attack by endopeptidases. Further, page 6 states that an advantage of the invention is that strong specific binding interactions can be achieved with conjugates in which the head groups are small in comparison to conventional biological receptors. Accordingly, in my opinion a skilled person would construe the head groups of the present invention in light of the description to be any small chemical or biological group but they do not include long peptide chains or a complete biological receptor. Preferably, the head groups according to the present invention are oligopeptides and the length of each peptide chain would not normally exceed ten amino acids, preferably six or less. Further, the head groups of the present invention are only capable of forming an epitope in combination with one or more other head groups. Each head group does not individually contain an epitope.

9. The Examiner considers that the receptor domains of Crabtree fall within the scope of the head groups of the present invention. Crabtree discloses on page 31 that the receptor domains will be at least 50 amino acids. Further, each individual receptor domain in Crabtree contains a complete epitope and can bind to a ligand. Accordingly, in my opinion the receptor domain in the chimeric protein of Crabtree is not a head group according to the present invention because it is too large and each receptor domain individually contains an epitope.

10. The Examiner considers that the extracellular inducer binding domain (ECD) disclosed in Capon falls within the scope of the head group of the present invention. Capon discloses on page 27 that the proliferation signaling domain (PSD), extracellular clustering domain (ECD), effector function signaling domain (EFSD) and intracellular clustering domain (ICD) will generally be from about 50 to 1500 amino acids. Further, each extracellular inducer-responsive clustering domain binds to at least one extracellular inducer moledule (see page 6). Accordingly, in my opinion the ECD in the chimeric protein of Capon is not a head group according to the present invention because it is too large and each ECD individually contains an epitope.

11. The Examiner considers that the variable domain sequences of the chimeric polypeptides disclosed in Ueda fall within the scope of the head groups of the present invention. Ueda discloses variable region sequences V_H and V_L domains. Single domain antibodies consisting of either V_H or V_L typically contain 70 amino acids, so these also are very much larger than the headgroups described in the present invention.

12. The Examiner considers that the chimeric proteins of Crabtree, Capon and Ueda fall within the scope of the conjugate of the present invention. For the same reasons provided in sections 8 to 11 above, in my opinion a skilled person would construe the term "conjugate" in the claims of the present invention to cover head groups of small chemical or biological groups linked to hydrophobic tail groups and not cover long peptide chains. Accordingly, in my opinion the proteins according to Crabtree, Capon and Ueda do not fall within the scope of the conjugates of the present invention.

13. In my opinion, there is no motivation or incentive for the skilled person to modify the proteins of Crabtree, Capon or Ueda to make them with smaller peptide domains which are capable of forming a distinct non-

covalent association in which the head groups are capable of positioning to form an epitope with higher affinity to a ligand than each of the head groups individually. In the present invention, the structure of the conjugates allows them to move freely in the micelle and the head groups can associate to form an epitope in the presence of a ligand. This provides an easier, quicker and cheaper way to identify the most favourable sequence for binding to a specific receptor compared to traditional combinatorial chemistry. The small head groups of the conjugates of the present invention also allows them to be far less immunogenic than their protein counterparts. The proteins of Crabtree, Capon and Ueda could not be used to identify the most favourable sequence for binding to a specific receptor because each protein already comprises an epitope which binds to a specific ligand. Crabtree, Capon or Ueda are not concerned with identifying sequences which bind to a ligand and provide no motivation for the skilled person to adapt the chimeric proteins so that they would be suitable for such a purpose.

14. In my opinion, even if the skilled person combined the teaching of Crabtree, Capon or Ueda with Onyuksel, they would not still arrive at the present invention because Onyuksel is concerned with the use of a biologically active amphipathic compound, such as VIP growth hormone. Onyuksel does not teach the skilled person to use the conjugates according to the present invention wherein the head groups form an epitope together by association which has higher affinity to a ligand than each of the head groups individually. As for Crabtree, Capon and Ueda, the active amphiphathic compounds could not be used in a combinatorial approach to identify the most favourable sequence for binding to a specific receptor.

15. Secondly, the proteins disclosed in Crabtree, Capon or Ueda are produced by introducing constructs comprising DNA encoding the proteins into cells and allowing the cells to express the proteins. Accordingly, in my opinion the skilled person carrying out the teaching of Crabtree would not inevitably produce isolated chimeric proteins. In contrast, the micelles according to claim 32 are in isolated form, which allows them to be used to identify the most favourable head group combination for binding to a specific receptor. In my opinion, the skilled person is provided with no motivation to provide the proteins of Crabtree, Capon or Ueda in isolated form because the skilled person is taught by these documents that it is essential for the proteins to be expressed in

cells in order for them to have the desired biological effect on the cell e.g. induction of apoptosis or proliferation.

16. Thirdly, a skilled person would have to modify the proteins of Crabtree, Capon or Ueda to make them capable of forming a micelle. In my opinion the proteins disclosed in Crabtree, Capon and Ueda are not capable of forming a micelle. The size ratio of hydrophilic to hydrophobic region of the molecules is so large that steric hindrance will prevent the hydrophilic regions to pack together closely enough to allow the hydrophobic portions to associate adequately. In some cases both ends of the molecule are hydrophilic, with only a hydrophobic central portion, which is not a structural configuration conducive to formation of micelles.

17. Fourthly, as acknowledged by the Examiner on page 14 of the Office Action, Crabtree, Capon or Ueda do not teach micelles of conjugates. It should be noted that micelles are usually defined as spherical colloidal structures which have a lipidic core and a surface composed of hydrophilic headgroups. Clearly, the cells described in Crabtree do not fit within this description. In many cases, the size of each of the individual protein molecules disclosed by Crabtree, Capon and Ueda can be equivalent to that of an entire micelle. In order to modify the teachings of Crabtree, Capon and Ueda to achieve the outcome described in the present invention, one would need to reduce in size and completely redesign the headgroups, use different chemical moieties to form the hydrophobic portions of the constructs, employ different synthetic strategies to form the headgroups, and use different chemistry for synthesis and assembly of the constructs, each with distinctly different chemical functionalities in terms of binding, in order to create the library of different micelles required to enable one to perform the screening process. The peptides attached to the surface of the micelles described in Onyuksel are also larger than described in the present invention, and because of this size, structure, and method of adherence to micelles, do not have sufficient flexibility or freedom of movement to allow adjacent peptides to come together in all possible configurations to enable formation of new epitopes. Thus, Onyuksel does not provide any guidance as to how, or why Crabtree, Capon and Ueda should be modified to achieve the objectives of the present invention.

18. A skilled person reading Crabtree, Capon and Ueda in view of Onyuksel would, in my opinion, not be provided

with any motivation to modify the teaching of these documents to arrive at a micelle according to claim 32. The Examiner refers to a passage in Onyuksel at column 11 which states that the micellar formulations of the invention deliver and enhance the bioactivity of the biologically active peptides in a manner which provides improvements in the efficacy and duration of the biological effects of the associated peptides. In my opinion, the skilled person would not be motivated to adapt the proteins of Crabtree, Capon and Ueda to make them capable of forming micelles and provide them in isolated form in a micelle in view of this teaching in Onyuksel because this goes against the teaching of Crabtree, Capon and Ueda to express the proteins in the cell membrane. Further, even if the skilled person did modify the proteins to make them capable of forming micelles and decide to construct micelles from the proteins, the skilled person would still not arrive at the present invention because the proteins would have to be modified to fall within the scope of the conjugates and head groups of the present invention, as discussed above in paragraphs 7 to 17. Accordingly, the combined teaching of Crabtree, Capon or Ueda and Onyuksel does not lead the skilled person to the micelle of claim 32.

19. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dr Roger Randal Charles New

Date: 5th September 2007

1408309

ROGER RANDAL CHARLES NEW: CURRICULUM VITAE

PERSONAL DETAILS

DATE OF BIRTH: 12 December 1950

HOME ADDRESS: Flat 10, Leinster Mansions
1 Langland Gardens
London Mob +447818068012
NW3 6QB e-mail: rogernew@proximaconcepts.com

NATIONALITY: English.

MARITAL STATUS: Married

LANGUAGES: English (native), Mandarin Chinese, Portuguese Russian & French.

N. I. NUMBER: WK065869A

WORK ADDRESS: Proxima Concepts Limited
c/o London Bioscience Innovation Centre
2 Royal College Street Tel: 44 20 7419 5980
London NW1 0TU Fax: 44 20 7419 5980

EDUCATION

1961 - 68 Manchester Grammar School

1968 - 72 Brasenose College Oxford, BA (Chemistry)

1972 - 75 St Mary's Hospital, London, PhD (Immunology)

EMPLOYMENT

1975 - 78 Dept of Biochemistry, Liverpool University, Senior Demonstrator

1978 - 83 Liverpool School of Tropical Medicine, Sen. Research Fellow on WHO grant

1983 - 85 Hon Lecturer at LSTM, Visiting Scholar, Jinan University, Guangzhou, People's Republic of China

1985 - 88 Leverhulme Senior Research Fellow, Liverpool School of Tropical Medicine

1988 - 90 Senior Scientific Officer, Liposomal-Doxorubicin Clinical Trial Programme

1990 - 92 Biocompatibles Ltd, Group Manager (Biointeractions)

1992 - 99 Cortecs Ltd, Director of Research (Oral peptide delivery)

2000 - Proxima Concepts Ltd, Executive Director & Co-founder

2003 - Diabetology Ltd, Chief Scientific Officer & Co-founder

PAST AND PRESENT RESEARCH ACTIVITIES

1. Liposomes

- The use of liposomes to improve therapy of infectious diseases, particularly leishmaniasis, hydatidosis and malaria. New methods of immunisation, using liposomes and other carriers to stimulate local and parenteral immune responses against infectious organisms and biological toxins, such as snake venoms. Encapsulation methods for stabilisation of liposomes and other delivery agents.

- Design of manufacturing suite for production of liposomes for testing in human patients. Manufacture and quality control of doxorubicin-containing liposomes for use in a clinical trial against liver metastatic cancer. Manufacture of liposomes containing cytosine arabinoside for pharmacokinetic study in leukaemia patients.

- Interactions of proteins and cells with biological membranes and synthetic surfaces. Development of tests for biocompatibility of biomaterials. Use of phospholipids to promote biocompatibility of synthetic materials.

- EEC and British Council supported project in Northwest China to study epidemiology, treatment and prevention of hydatidosis in rural populations. Development of liposomal formulation of albendazole to improve bioavailability of this drug for treatment of echinococcosis. Human clinical trial at planning stage.

- Collaboration with OSEAN-supported group in Mahidon Institute for Tropical Diseases, Bangkok (1983 and 1986) on oral cholera vaccines administered in liposomes.

- Publication of over thirty peer-reviewed articles in scientific journals (including *Nature*, *The Lancet* and *New England Journal of Medicine*). Author of the book "Liposomes – A Practical Approach" OUP, and miscellaneous chapters and patents.

2. Oral peptide Delivery

- Development of delivery systems based on neutral oils for transport of macromolecules across the gut wall, stimulation of immunity and other applications.

- Head of a research team for eight years specialising in developing new methods for enhancement of uptake of macromolecules across the gut. Special attention was paid to the use of lipids, since these are well taken up by the gastro-intestinal tract.

- Inventor of two different technologies for formulation of macromolecules in oil phases. Preparations obtained using this technology can be constructed using well-charcterised pharmacuetical excipients, are inexpensive and amenable to scale-up, and are well-tolerated upon administration to animals and humans.

- These formulation technologies have been applied to construct vehicles which can enhance uptake of macromolecules (calcitonin and insulin) across the small intestine in animals. Materials can cross either via the trans-cellular or paracellular routes, depending on the oils employed.

- Have also devised several novel *encapsulation* methodologies for facilitating administration of oil-based formulations via oral and other routes.

- Formulations constructed using both technologies described above have been tested in human clinical trials with type I and type II diabetic patients, as well as normal volunteers. Insulin derived from the formulations has been detected in the bloodstream after administration of commercially viable quantities of insulin via the intestine.

- Variations of these formulations have been developed which can modulate the immune response to encapsulated antigens after oral administration.

- Extensive experience acquired in setting up and running of animal (catheterised pig/rodent) and *in vitro* models (range of monolayer transwell cell cultures) for intestinal transport.

- Development of improved nutritional supplements for enhancing the growth and survival of early stage fish larvae important in the marine aquaculture industry (collaboration with Singapore).

- Patents applied for or granted:
  WO 95/13795 (accepted for grant in Europe); WO 96/17593; WO 96/17593;
  WO 96/14871; GB 96/02615; GB 96/02751; GB 97/00749; GB 97/01775;
  UK Application 9826822.0; UK Application 9826821.2

- Additional approaches to formulation of improved oral delivery vehicles which do not rely on the proprietary technology described above are under consideration.

3. International Activities

- Lived and worked in China for two years as scientist in Chinese research institute (Jinan University Medical School 1983-85). Good knowledge of Mandarin – both reading and spoken.

- Participated in multicentre research collaboration on hydatid disease in North China (1986 – present day) suported by British Council, EEC, Royal Society and Wellcome Trust. Appointed visiting professor at Xinjiang Medical School, PRC. Provided training for three PhD students.

- Selected by British government to represent UK in two expert missions to China on biotechnology (1996 & 1998).

- Sent as expert scientist by Canadian aid organisation IDCR to report on status of scientific research in Burma (now Myanmar).

- Lived and worked in Bangkok (Mahidon Institute for Tropical Diseases) 1983 and 1986 on oral cholera vaccines. Supervised MSc project in OSEAN training programme.

- Have devised and run workshops on liposomes in Colombia, and been invited to participate in workshops in Portugal and Denmark.

- On-going collaborations with, Cartgena, Colombia (pulmonary fibrosis), Singapore (vaccines for fish larvae), University of Queensland (peptide epitopes) and FUNED in Belo Horizonte, Brazil (snake venom vaccine).

EXPERIENCE IN INDUSTRY

- Ten years experience in industry in managerial roles, reporting directly to the CEO.
- Responsible for a budget of US$1 million/annum.
- Instrumental in setting up research facilities from scratch for conducting a wide range of *in vitro* and *in vivo* analytical and formulation pharmaceutics activities.
- In charge of a group of 10-15 scientists conducting work ranging from basic research to clinical manufacture, under conditions conforming to the code of Good Laboratory Practice.
- Responsible for progression of experimental formulations right from early concept stage at laboratory bench to proof of principle in human clinical trial.
- Have direct experience of manufacture of formulations to GMP for clinical trial supplies.
- Acquired extensive project and man management expertise, working with a fully integrated team responsible for strategic planning of company activities. Good interpersonal skills.
- Responsible for spearheading the presentation of technology to multinational client companies, and in major international scientific arenas.
- Intimate understanding of requirements which need to be fulfilled in order for a product to be registered and receive regulatory approval.
- Involved in writing, filing, prosecution and defence of patents (over ten filed in own name).

PRESENTATIONS AT SCIENTIFIC MEETINGS

Apr 1974	British Soc Immunology, London "*Induction of Specific Unresponsiveness to Transplantation Antigens in Mice*"
June 1974	Int Congress Transplantation, Jerusalem "*Studies on the Mechanism of Specific Unresponsiveness to Skin Allografts*"
June 1978	Gordon Conf on "Drug Carriers in Med & Biology" USA "*Treatment of Leishmaniasis by Liposome-entrapped Antimonial Compounds*"
Sep 1979	Harden Conf, Wye College, Kent, UK on "Delivery and Targeting of Therapeutic Agents with Particular Reference to Liposomes" "*Leishmaniasis*"
Mar 1980	Joint Meeting of Royal Soc of Tropical Med & Hyg with Swiss Soc for Trop Med & Parasitol, Basel "*The Treatment of Experimental Cutaneous Leishmaniasis by Liposome-entrapped Antimonials*"
	Also chaired workshop on Drug Carriers
June 1980	Brit Nuclear Med Soc Annual Congress, London "*Distribution of Liposomes in Inflamed Tissue*"
Jul 1980	Janssen Symp on "Biochemistry of Parasites", Antwerp "*The Treatment of Leishmaniasis by Liposome-entrapped Compounds*"
May 1981	Symp: "Drug Carriers in Radiobiol.", Nottingham UK "*Distribution of Liposome-entrapped Antimonials in Experimental Models for Visceral and Cutaneous Leishmaniasis*"

Sep 1981	Conference on "Liposomes in Biology", Grignon France *"Leishmaniasis and Liposome"*
Sep 1982	Conference on "Liposome Technology", San Francisco *"Liposome Therapy for Leishmaniasis"*
Sep 1983	Conference on "Liposomes in Medicine", Grignon *"Leishmaniasis & Liposomes - Latest Developments"*
Jul 1984	Gordon Conference on "Drug Carriers", Plymouth USA *"Entrapment of Snake Venoms inside Liposomes"*
Jul 1985	National Conference on Parasitology in Shandong Province, China *"Improved Therapy for Leishmaniasis"*
Nov 1988	National Hydatid Group Meeting, Nottingham, UK *"Hydatid Disease in China"*
Apr 1989	BPI/BPS Seminar School on "Targeting and Delivery of Immunologic Agents" London UK. Invited Speaker on *"Stimulation of Immunity by Oral Administration of Liposomes"*
May 1989	International Symposium on Natural Toxins, Guilin, China 1. *"Stimulation of Parenteral Immunity against Snake Venoms by Liposomal Vaccination"* 2. *"Stimulation of Immunity by Oral Administration of Liposomes"*
Feb 1990	Conference: "Liposome Research Days" Gainesville, Florida. Session Chairman and invited speaker. *"Liposomes in Chemotherapy and Immuno-therapy in Tropical Medicine".*
Dec 1990	Conference: "Liposomes 21 Years On" *"Liposome Encapsulation System for Shrimp Larval Microdiets".*
July 1991	Gordon Conference on "Biomaterials and Biocompatibility" Plymouth , New Hampshire. *"Increase in Biocompatibility of Polymer by Treatment with Phosphatidyl Choline".*
Dec 1991	Material Research Society, Fall Meeting, Boston USA *"A New Platelet Enzyme Immunoassay for Assessment of Biocompatibility in vitro."*

Feb 1993 — Sixth Symposium on Recent Advances in Drug Delivery Systems, Salt Lake City, Utah
"Efficacy of Albendazole Administered Orally is Improved by Encapsulation in Liposomes."

Feb 1993 — Sixth Symposium on Recent Advances in Drug Delivery Systems, Salt Lake City, Utah
"Use of a Lipid Carrier to Deliver Calcitonin via the Small Intestine"

April 1994 — Third European symposium on Controlled Drug Delivery
"Changes in Urinary Crosslinks After Administration of Calcitonin to Humans by Intranasal and Oral Routes"

June 1994 — 21st International Symposium on Controlled Release of Bioactive Materials, Nice, France
"Changes in Urinary Crosslinks After Administration of Calcitonin to Humans by Subcutaneous and Oral Routes."

Dec 1994 — Groupe Thematique de Recherche sur les Vecteurs.
Session Chairman and Invited Speaker
"Lipidic Delivery Systems for Macromolecules"

Aug 1995 — 22nd International Symposium on Controlled Release of Bioactive Materials, Seattle, USA
"Oral Administration of Tetanus Toxoid in an Oil-based Carrier for Stimulation of a Systemic Immune Response."

Aug 1995 — 22nd International Symposium on Controlled Release of Bioactive Materials, Seattle, USA
"Macrosol – a New Oil-based Carrier Vehicle."

July 1996 — 23rd International Symposium on Controlled Release of Bioactive Materials, Kyoto, Japan
"The Use of Macrosol Technology for Highly Effective Antioxidant Protection of Unsaturated Oils."

July 1996 — 23rd International Symposium on Controlled Release of Bioactive Materials, Kyoto, Japan
"Use of an Oil-Phase Carrier – Macrosol – for Intestinal Delivery of Peptides in Large Animals."

May 1997	AIC Conference on Oral and Mucosal Delivery Systmes for Macromolecules, London UK *"Oral Delivery of Peptide Hormones Using the Oil-based Carrier 'Macrosol'."*
June 1997	24th International Symposium on Controlled Release of Bioactive Materials, Stockholm, Sweden *"Enteral Delivery of Insulin in Normal Humans Using an Oil-based Macrosol Formulation."*
June 1997	24th International Symposium on Controlled Release of Bioactive Materials, Stockholm, Sweden *"Oral Administration of a Macrosol Formulation can Stimulate Immunity Against Plague Antigens."*
Sep 1997	Recent Advances in Drug Delivery Science and Technology, Beijing, China *"Enteral Delivery of Insulin in Normal Humans Using an Oil-based Macrosol Formulation."*
May 1999	United Kingdom Association of Pharmaceutical Sciences symposium on Current Issues in Peptides and Proteins. Invited Speaker *"Oral Peptide Delivery"*

PUBLICATIONS

New RRC, Richards WG. *Nature New Biology* **237** p214 (1972)

Molecular Orbital Study of Hapten-Antibody Interactions

Brookes CG, Brent L, Kilshaw PJ, New RRC, Pinto M. *Transpl* **19** p134 (1975)

Specific Unresponsiveness to Skin Allografts in Mice

Kilshaw PJ, Brent L, Brooks CG, New RRC, Pinto M. *Trans Proc VII* p385 (1975)

Studies on the Mechanisms of Specific Unresponsiveness to Skin Allografts in Mice

New RRC, Chance, ML, Thomas SC, Peters W. *Nature* **272** p55 (1978)

Antileishmanial Activity of Antimonials Entrapped in Liposomes

Chance ML, New RRC, Thomas SC, Heath S. *Tr Roy Soc Trop Med Hyg* **73** p321 (79)

The Treatment of Visceral Leishmaniasis with Liposomes

New RRC, Chance ML. *Acta Tropica* **37** p253-6 (1980)

The Treatment of Experimental Cutaneous Leishmaniasis by Liposome-Entrapped Antimonials

Chance ML, New RRC. Proceedings of Janssen Symposium on Biochemistry of Parasites, North Holland 1980 ed H van den Bossche

The Use of Liposomes in the Treatment of Experimental Cutaneous and Visceral Leishmaniasis

New RRC, Critchley M, Gulliford P. *Nuc Med Comm* **1** p154 (1980)

The Distribution of Liposomes in Inflamed Tissue

New RRC, Chance ML, Heath S. *Parasitology* **83** p519 (1981)

Liposome Therapy of Cutaneous Leishmaniasis: Dependence on Time and Route of Administration

New RRC, Chance ML, Heath S. J *Antimicrobial Chemotherapy* **8** p371 (1981)

Antileishmanial Activity of Amphotericin and Other Antifungal Agents Entrapped in Liposomes

New RRC, Chance ML, Critchley M in "Radionuclide Imaging Drug Research" Ed Wilson CG et al Croom Helm London (1981) p279

The Distribution of Radio-labelled Drug in Animals Infected with Cutaneous and Visceral Leishmaniasis

New RRC, Chance ML, Heath S. *Biol Cell* **47** p59 (1983)

Liposome Therapy for Experimental Cutaneous and Visceral Leishmaniasis

Heath S, Chance, New RRC. *Molec & Biochem Parasitol* **12** p49 (1984)

Quantitative and Ultrastructural Studies on the Uptake of Drug-loaded Liposomes by Mononuclear Phagocytes Infected with *Leishmania donovani*

Chance ML, New RRC. Brit Soc Myc Symp "Mode of Action of Antifungal Agents" Ed APJ Trinci & JF Ryley (1984) p377

Enhancement of Efficacy of Antifungal Agents by Entrapment inside Liposomes

New RRC, Theakston RDG, Zumbuhl O, Iddon D, Friend J. *NEJM* **113** p56 (1984)

Immunisation Against Snake Venoms

New RRC, Theakston RDG, Zumbuhl O, Iddon D, Friend J. *Toxicon* **23** p215 (1985)

Liposomal Immunisation Against Snake Venoms

Theakston RDG, Zumbuhl O, New RRC. *Toxicon* **23** p925 (1985)

Use of Liposomes for Protective Immunisation Against Snake Venom in Sheep

Laing G, Theakston RDG, New RRC, Zumbuhl O & Parsley A. *Trans Roy Soc Trop Med & Hyg* **80** p338 (1986)

Use of Liposomes Incorporating Immunostimulant for Immunisation against Snake Venoms

Zumbuhl O, Theakston RDG, New RRC, Iddon D & Friend J in "Liposomes as Drug Carriers" Ed Schmidt KH. Georg Thieme Verlag Stuttgart, NY pp214-232 (1986)

Liposomes as Adjuvants for Immunisation Against Snake Venoms

Laing G, Theakston RDG & New RRC. Proceedings of 1st Asia Pacific Congress on Animal, Plant & Microbiol Toxins. Singapore June 1987

Use of Liposomes Incorporating Immunostimulant for Parenteral and Oral Immunisation Against Snake Venom

Sells RA, Owen RR, New RRC, Gilmore IT. *Lancet* No 8559 pp624-5 (1987)

Reduction in Toxicity of Adriamycin by Liposomal Entrapment

Sells RA, Gilmore IT, Owen RR, New RRC & Stringer RE. *Cancer Treatment Rev* **14** pp383-387 (1988)

Reduction in Doxorubicin Toxicity following Liposomal Delivery

Freitas TV, Tavares AP, Theakston RDG, Laing G & New RRC. Toxicon **27** pp341-347 (1989)

Use of Liposomes for Protective Immunisation against *Crotalus durissus* (Tropical rattlesnake) Venom

Price G, Aherne W, New RRC, Mayhew E, Stringer RE, Littleton P, Adams K, Rustum Y & Lister A. *Proc Am Assoc Cancer Res* **30** p988 (1989)

Encapsulation of cytosine arabinoside in liposomes: a method of manipulating *in vivo* pharmacokinetics in man

Chaicumpa W Parairo JR New RC Pongponratn E Ruangkunaporn Y Tapchaisri P & Chongsanguan M *Asian Pac J Allergy Immunol* **8** pp87-94 (1990)

Immunogenicity of liposome-associated oral cholera vaccine prepared from combined *Vibrio cholerae* antigens.

Wen H New RR Craig PS *Br J Clin Pharmacol* **35** pp565-74 (1993)

Diagnosis and treatment of human hydatidosis.

Groth T Klosz K Campbell EJ New RR Hall B & Goering H J *Biomater Sci Polym Ed* **6** pp497-510 (1994)

Protein adsorption, lymphocyte adhesion and platelet adhesion/activation on polyurethane ureas is related to hard segment content and composition.

Wen H, Zhang HW, Muhmut M, Zou PF, New RRC & Craig PS. *Ann Trop Med Parasitol* 88 pp49-52 (1994)

Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis.

Wen H Zou PF Yang WG Lu J Wang YH Zhang JH New RR & Craig PS *Trans R Soc Trop Med Hyg* 88 pp340-3 (1994)

Albendazole chemotherapy for human cystic and alveolar echinococcosisin north-western China.

Wen H New RR Muhmut M Wang JH Wang YH Zhang JH Shao YM & Craig PS *Parasitology* 113 pp111-21 (1996)

Pharmacology and efficacy of liposome-entrapped albendazole in experimental secondary alveolar echinococcosis and effect of co- administration with cimetidine.

New RRC, Littlewood G, Guard P Browning I & Hotten B. *Intl J Pharm* 156 pp1-8 (1997)

Intestinal delivery of calcitonin in pig

In Press

M.O. Domingos, K.C. Barbaro, W. Tynan, J. Penny, D.J.M. Lewis, R.R.C. New. *Toxicon* 42(5):471-9 (2003)

Influence of sphingomyelin and TNF-alpha release on lethality and local inflammatory reaction induced by *Loxosceles gaucho* spider venom in mice.

M.O. Domingos, W. Tynan, K.C. Barbaro, J. Penny, D.J.M. Lewis, R.R.C. New. *Toxicon* 42(4):439-45 (2003)

Effect of *Loxosceles gaucho* venom on cell morphology and behaviour in vitro in the presence and absence of sphingomyelin.

CHAPTERS CONTRIBUTED

New RRC in "Phospholipids Handbook" Ed G Cevc, Marcel Dekker, NY 1993

Biotechnological Applications of Phospholipids

New RRC in "Liposomes as Tools in Basic Research and Industry" Eds JR Philippot & F Schuber, CRC Press, Boca Raton 1995

Influence of Liposome Characteristics on Their Properties and Fate

New RRC in "Encyclopaedia of Molecular Biology", VCH Publishers, NY 1995

Liposomal Vectors

New RRC & Kirby CJ in Advanced Drug Delivery Reviews 25 pp59-69 (1997)

Solubilisation of hydrophilic drugs in oily formulations

BOOKS PUBLISHED

New RRC (Editor & Author)

"Liposomes: A Practical Approach"
OUP UK (1989)

Numerous patents pending and granted.

EXPERIENCE OVERSEAS

1. Lived and worked in China for two years as scientist in Chinese research institute (Jinan University Medical School 1983-85). Good knowledge of Mandarin – both reading and spoken.

2. Participated in multicentre research collaboration on hydatid disease in North China (1986 – present day) suported by British Council, EEC, Royal Society and Wellcome Trust. Appointed visiting professor at Xinjiang Medical School, PRC. Provided training for three PhD students.

3. Member of two high-level delegations sent to China by British government to report on biotechnology in China.

4. Lived and worked in Bangkok (Mahidon Institute for Tropical Diseases) 1983 and 1986 on oral cholera vaccines. Supervised MSc project in OSEAN training programme.

6. Acted as consultant to IDRC (Canada) to review programmes supported in Burma (now Myanmar) on snake venom vaccination.

5. Devised and run scientific workshops in Colombia (1998). On-going collaborations with, Cartgena, Colombia (pulmonary fibrosis), Singapore (vaccines for fish larvae), University of Queensland (peptide epitopes) and FUNED in Belo Horizonte, Brazil (snake venom vaccine) – fluent in Portuguese.

PAST AND PRESENT RESEARCH ACTIVITIES

1. The use of liposomes to improve therapy of infectious diseases, particularly leishmaniasis, hydatidosis and malaria. New methods of immunisation, using liposomes and other carriers to stimulate local and parenteral immune responses against infectious organisms and biological toxins, such as snake venoms. Encapsulation methods for stabilisation of liposomes and other delivery agents.

2. Design of manufacturing suite for production of liposomes for testing in human patients. Manufacture and quality control of doxorubicin-containing liposomes for use in a clinical trial against liver metastatic cancer. Manufacture of liposomes containing cytosin arabinoside for pharmacokinetic study in leukaemia patients.

3. Interactions of proteins and cells with biological membranes and synthetic surfaces. Development of tests for biocompatibility of biomaterials. Use of phospholipids to promote biocompatibility of synthetic materials.

4. EEC and British Council supported project in Northwest China to study epidemiology, treatment and prevention of hydatidosis in rural populations. Development of liposomal formulation of albendazole to improve bioavailability of this drug for treatment of echinococcosis. Human clinical trial at planning stage.

5 Development of improved nutritional supplements for enhancing the growth and survival of early stage fish larvae important in the marine aquaculture industry (collaboration with Singapore).

6. Development of delivery systems based on neutral oils for transport of macromolecules across the gut wall, stimulation of immunity and other applications.

7. Publication of over thirty peer-reviewed articles in scientific journals. Author of the book "Liposomes – A Practical Approach" OUP, and miscellaneous chapters and patents. Have devised and run workshops on liposomes in Colombia, and invited to participate in workshops in Portugal and Denmark.

8. Selected by British government to represent UK in expert missions to China on biotechnology. Sent as expert scientist by Canadian aid organisation IDCR to report on status of scientific research in Burma (now Myanmar).

EXPERTISE IN FACILITATING ABSORPTION ACROSS G.I.T

- Was Head of a research team for eight years specialising in developing new methods for enhancement of uptake of macromolecules across the gut. Special attention was paid to the use of lipids, since these are well taken up by the gastro-intestinal tract.

- Am inventor of two different technologies for formulation of macromolecules in oil phases. Preparations obtained using this technology can be constructed using well-charcterised pharmacuetical excipients, are inexpensive and amenable to scale-up, and are well-tolerated upon administration to animals and humans.

- These formulation technologies have been applied to construct vehicles which can enhance uptake of macromolecules (calcitonin and insulin) across the small intestine in animals. Materials can cross either via the trans-cellular or paracellular routes, depending on the oils employed.

- Have also devised several novel encapsulation methodologies for facilitating administration of oil-based formulations via oral and other routes.

- Formulations constructed using both technologies described above have been tested in human clinical trials with type I and type II diabetic patients, as well as normal volunteers. Insulin derived from the formulations has been detected in the bloodstream after administration of commercially viable quantities of insulin via the intestine.

- Variations of these formulations have been developed which can modulate the immune response to encapsulated antigens after oral administration.

- Extensive experience has been acquired in setting up and running of animal (catheterised pig/rodent) and *in vitro* models (range of monolayer transwell cell cultures) for intestinal transport.

- Have participated directly in manufacture of formulations to GMP for clinical trial supplies.

- Additional approaches to formulation of improved oral delivery vehicles which do not rely on the proprietary technology described above are under consideration.

- Patents applied for or granted:

  WO 95/13795 (accepted for grant in Europe); WO 96/17593; WO 96/17593; WO 96/14871; GB 96/02615; GB 96/02751; GB 97/00749; GB 97/01775; UK Application 9826822.0; UK Application 9826821.2